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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/516,553 | 11/30/2004 | Tadaaki Yabubayashi | 09853/0202140-US0 | 7061 |

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| EXAMINER | |
|---|---|
| POHNERT, STEVEN C | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

| MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/516,553 | YABUBAYASHI ET AL. | |
| | Examiner | Art Unit | |
| | Steven C. Pohnert | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5-9,11-14 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9,11-14 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/2008 has been entered.

### Claim status

The response has canceled claims 1-4, 10, 15-22.

The amendment has made all pending claims dependent on newly added claims 24-27.

The 112-2$^{nd}$ paragraph rejection has been withdrawn due to the amendment to the claims.

Claims 5-9, 11-14, 23-27 are pending.

### *Sequence Compliance*

The application fails to comply with CFR 1.821(d), which states:

(d)Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, figures 1-5, contains a nucleic acid sequence. Applicant is required to check the rest of the disclosure for any other nucleic acid or protein sequences and list them in a sequence listing and identify them with a proper SEQ ID NO.

The specification and sequence listing must be amended to bring it into sequence compliance. **For any response to this office action to be fully compliant, the response has to bring the application in compliance with sequence rules.**

***Drawings***

2. The drawings are objected to because the drawing contain nucleic acid sequences longer than 10 nucleotides corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Alternatively the specification can be amended in the description of drawings to clearly indicate the SEQ ID NO associated with each nucleic acid sequence. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after

the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

### *Claim Objections*

3. Applicant is advised that should claims 24 and 25 be found allowable, claims 26 and 27 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 5-14, 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al (WO/1999/31275, Published June 24, 1999) in view of Blackburn et al

(US Patent 6264825 issued July 24, 2001). This rejection has been modified to reflect the amendments to the claims.

The newly presented claims 24 and 26 have the limitations that the loop structure is "pre-modified." The limitation that the structure be pre-modified is being given the broadest reasonable interpretation that the structure is modified by a label prior to the penultimate step of an assay.

The newly presented claims 24 and 26 have the limitations that the loop structure is "principal part of said loop-structured nucleic acid which binds complementarily with a biochemical specimen is located on the substrate side." The limitation, "principal part of said loop-structured nucleic acid which binds complementarily with a biochemical specimen is located on the substrate side" is being given the broadest reasonable interpretation that the specimen binding region of the nucleic acid is on or near a substrate.

With regards to claim 24 and 26, Gold et al teach teaches the use of mutually complementary nucleic acids for detection of binding of a target molecule to a nucleic acid ligand (see page 20, lines 26-30). Gold teaches the detection of ligand binding by electronic means (see abstract) and further teaches the use of gold or silver as the substrate for the array (see page 12, line 30). Thus the gold or silver of Gold allow for detection by the transfer of electrons and thus are electrodes (see page 26, lines 7-31). Gold further teaches, " an insulative silica "gate" is placed between two n-type semiconductors, forming a biochip. Current will flow from one semiconductor to the other when a conducting channel is formed in the gate and a potential difference is

applied" (see page 26, lines 9-14). Gold et al teaches a target molecule is a nucleic acid (see page 6, lines 11-15). Gold teaches that ligands are bound to discrete locations (see page 26, lines 14-15). Gold further teaches that upon targeting molecule binding to the nucleic acid ligand a conformation change occurs that allows hybridization of further nucleic acid molecules to the nucleic acid ligand (page 20, lines 28-30). Gold thus teaches that a free end of the loop structure nuclei acid probe is not fixed on the surface of the substrate. Gold teaches the nucleic acid molecules further modifying the nucleic acid ligand also undergo a conformational change allowing the formation of an intermolecular hybridization complex to form (see page 20, line 30-page 21, line 5). Gold further teaches the mutually complementary nucleic acids are stem-loop nucleic acids on the surface of the chip (see page 21, lines 15-16 and figure 6). Gold further teaches that scaling up of technology accurately allows the measurement of thousands of discrete changes in current drain (see page 26, line 23).

With regards to claims 25 and 27, Gold teaches the use of an intercalating dye by scanning before and after addition of test sample (see page 24, lines 9-11). Gold thus teaches a method during or after hybridization as the intercalating dye is only visible upon intercalation.

With regards to claim 5 and 6, Gold teaches binding of the target molecule results in a net loss or gain of ions at that region of the chip, altering conductance and a current drain in this area of the chip (see page 26, lines 16-22). Gold's teaching of detecting alterations in current conductance after the addition of a target ligand

inherently requires that the conductance before addition of the ligand is known. Gold thus teaches the detection and quantification before and after hybridization.

With regards to claims 8 and 9, Gold teaches the thiolpropionate having a photochemical reactive group is couple to functional groups on the surface of the biochip (see page 13, lines 8-10). Gold further teaches light of the appropriate wavelength, followed by the attachment to substrate (see page 13, lines 10-16) and the unbound nucleic acid is washed away. Gold further teaches the use of photoactivatable biotin (label) by a similar method (see page 13, lines 23-25).

Gold does not teach the label is a magnetic particle, ceramic fine particle or semiconductors (claims 24 and 26). Gold et al does not detection of the probes on each electrode prior to the hybridization with the biochemical reactant (claim 7). Gold et al does not teach detection of complex by electronic methods (claim 11). Gold et al does not teach detection/discrimination of the complex by electronic and magnetic methods (claim 12). Gold et al does not teach detection by electronic and optical methods (claim13). Gold et al does not teach detection by magnetic, optical and electronic means (claim 14).

However, Blackburn et al teaches a method of detecting an analyte by electron transfer moiety (ETM) (see abstract). Blackburn teaches that the ETM are labeled nucleic acids containing transition metals including iron (see column 45, lines 9-20). Iron is a magnetic particle. Blackburn et al further teaches the use of silicon containing moieties as labels (see column 27, line 1). Blackburn et al teaches the detection of the use of a plurality of gold electrodes (see column 2, lines 60-65). Blackburn further

teaches the detection of probes prior to any experiment for use as an internal control for calibration of an experiment (see column 48, lines 4-14) (claim 7). Blackburn teaches the enzymatic incorporation of an ETM (label) during PCR (see column 60, lines 8-11). Blackburn et al further teaches the detection of the presence of ETM on the surface of the electrodes by amperommetry, voltametry, capacitance or impedance (see column 81, lines 55-67) (claim 11).

With regards to claim 12, Blackburn teaches the use of magnetic particles can be used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines 33-39). Thus Blackburn's use of magnetic particles to selectively move the ligand complex to the electrodes where it is detected results in detection based on discrimination (movement on magnetic particles) and detection by electronic means at electrode.

With regards to claim 13, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80, line 47). Electrochemiluminesence is activation of chemilumensence by a current. Thus the increase in the current results in detection of an optical signal.

With regards to claim 14 and 23, Blackburn teaches the use of magnetic particles used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines 33-39). Further, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80,

line 47). Electrochemiluminesence is activation of chemilumensence by a current. Thus the increase in the current results in detection of an optical signal. Thus Blackburn teaches the detection/discrimination of a chemical reactant complex comprising the use of discriminating on magnetic signal, current values and optical. Thus Blackburn teaches detection of electrical and optical changes before and after hybridization.

Therefore it would have been prima facie obvious to one of ordinary skill in art at the time the invention was made to combine the hairpin probes of Gold with detection method of Blackburn, including Blackburn's metal (iron) and silicon containing labels. The skilled artisan would be motivated because Blackburn teaches his method allows concentration of the target ligand with the capture ligand maximizing interaction (see column 9, lines 37-40). The ordinary artisan would further be motivated as this allows very small samples to be analyzed (see column 81, lines 25-27). The ordinary artisan would be motivated to use Blackburn's method of internal control as it allows more accurate and quantitative detection. Thus the combined teachings of Gold and Blackburn would result in the ability to increase the sensitivity of the loop probes of Blackburn by concentrating the biochemical samples with the probes. The combined teachings would also allow for improved sensitivity because the quantization of the probes would result in a better determination of the limits of detection of the assay.

**Response to Arguments**

The response of 3/17/2008 asserts there is no reason (motivation) to combine the teachings of Gold and Blackburn. KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support obviousness. Further

as the examiner has suggested above and previously. "The skilled artisan would be motivated because Blackburn teaches his method allows concentration of the target ligand with the capture ligand maximizing interaction (see column 9, lines 37-40). The ordinary artisan would further be motivated as this allows very small samples to be analyzed (see column 81, lines 25-27). The ordinary artisan would be motivated to use Blackburn's method of internal control as it allows more accurate and quantitative detection. " Thus the artisan would be motivated to combine the teachings of Gold in Blackburn to improve the method of Gold.

The response further asserts that Blackburn does not teach the use of magnetic particles, ceramic fine particles, or semiconductors as labels and thus the use of these particles is not obvious over Gold. These arguments have been thoroughly reviewed but are not considered persuasive as Blackburn et al teaches the use of nucleic acids with silicon or iron attached (column 45, lines 9-20; column 27, line 1). Blackburn further teaches the use of magnetic particles (see column, 19, lines 33-39). Thus the teachings of Gold and Blackburn render the instant claims obvious. The response further asserts that Gold does not provide any reason (motivation) to position a free end so it is not fixed to the surface and principal part of the loop-structured nucleic acid which binds complementarily with a biochemical specimen is located on the substrate side. These arguments have been thoroughly reviewed but are not considered persuasive as Gold teaches such a structure (see page 21, lines 15-16 and figure 6) and thus no motivation is required. The specimen binding region is attached to the

substrate and thus the limitation is taught by Gold and the combination of Gold and Blackburn renders the instant claims obvious.

**Summary**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634